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DONOR AGE, COLD ISCHEMIA TIME, AND DELAYED GRAFT FUNCTION

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Running headline:

Donor Age and Delayed graft function

Abstract

Background and objectives: Increased donor age is one of the most important risk factors for delayed graft function (DGF), and previous studies suggest that the harmful effect of cold ischemia time is increased in kidneys from older donors. Our aim was to study the association of increased donor age and cold ischemia time with the risk of delayed graft function in a large cohort kidney transplants from the current era.

Design, setting, participants, and measurements: Scientific Registry of Transplant Recipients (SRTR) was used for this observational retrospective registry analysis to identify all deceased donor kidney transplantations in the US between 2010 and September 2018, who were on dialysis pretransplantation (N=90,810). The association of donor age and cold ischemia time with the risk of DGF was analyzed in multivariable models adjusted for recipient characteristics (age, race, gender, diabetes, cPRA, pretransplant dialysis duration) and donor characteristics (cause of death, gender, race, BMI, creatinine, donation after circulatory death status (DCD), history of hypertension, and HLA mismatch).

Results: Cold ischemia time and donor age were independently associated with the risk of DGF, but the risk of DGF was not statistically significantly lower in donor age categories between 50-64, compared to donors ≥65 years. The harmful association of cold ischemia time was not higher in kidneys from older donors in any age category, not even among donation after circulatory death donors. When donor risk was assessed with kidney donor profile index (KDPI), although a statistically significant interaction with cold ischemia time was found, no practically meaningful increase in the susceptibility of high KDPI kidneys to cold ischemia was found.

Conclusions: We were unable to demonstrate an association between donor age and DGF. The association of longer cold ischemia time with the risk of DGF was not magnified in older or more marginal donors.

Introduction

Delayed graft function (DGF) is estimated to occur in approximately 20-40% of patients after deceased donor kidney transplantation (1-3), and it is associated with increased length of hospital stay and costs after transplantation (4,5). DGF is also associated with an increased risk of acute rejection (6) and with impaired long-term outcome after kidney transplantation (6,7), although some studies have failed to show harmful long-term effects of DGF (8,9).

Delayed graft function is thought to originate from ischemia-reperfusion injury to the graft, and the most important risk factors for DGF are described to be increased donor age and increased cold ischemia time (1,10,11). Similarly, other factors that compromise the functional or reparative capacity of the graft have been associated with the risk of DGF, such as donation after circulatory death (DCD) (12), especially uncontrolled donation after circulatory death (13), presence of donor-specific antibodies (14), highly sensitized patients (10), or kidney dysfunction in the donor (10,11). The use of machine perfusion, on the other hand, has been associated with a lower incidence of DGF (15). In the recent years, the quality of deceased donors in the US has been assessed with the Kidney Donor Profile Index (KDPI) (16), and similar to high donor age, high KDPI has been associated with increased risk of DGF (17).

Several studies have shown that older kidneys may be more susceptible to the damage caused by cold storage (18-20), whereas no data exist about the possible more harmful effect of cold ischemia time on marginal kidneys when assessed with the KDPI scale.

Our aim was to study the association between donor age and the risk of DGF in the current era in a large cohort of deceased donor kidney transplant recipients, and to study whether the harmful association of longer cold ischemia with the risk of DGF is magnified in kidneys from older donors or kidneys from high KDPI donors.

Material and Methods

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. Standard Analysis Files (Q3 2018 release) were used. This study is a retrospective observational registry analysis. This study had the approval of the institutional review board of Helsinki University Hospital (HUS/333/2019). The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.

Patients

From the SRTR data, we identified all deceased donor kidney transplantations between 2010 and September 2018. The primary outcome was DGF, defined by the need of dialysis during the first posttransplant week, and therefore only patients with pretransplant dialysis treatment were included (N=90,810) in the primary analyses. Altogether 93 patients had the data about DGF missing, and were excluded from the analyses, resulting in a cohort of 90717 patients for the primary analyses.

Statistical analyses

Multivariable binary logistic regression was used to examine risk factors for DGF, with posttransplant dialysis during the first posttransplant week as the primary outcome. As our primary focus was to study the association of donor age and cold ischemia time on the risk of DGF, these variables were the primary effect variables in the models. Adjustment was made with covariates, which were significant in univariable logistic regression ($P<0.05$), or which were identified as risk factors for DGF in the previous literature. For the logistic regression models, the last available

cPRA (calculated panel-reactive antibodies) level was categorized to <80% (reference group), from 80% to <95%, from 95% to <99%, and ≥99%. The association of donor age with the risk of DGF was compared to age ≥65 years (reference group) and categorized between five-year increments until the age categories 12-19, 5-11, and 0-4 years. Cold ischemia time was categorized to 0-11hrs (reference group), 12-15 hours, 16-19 hours, 20-23 hours, and ≥24 hrs. Kidney donor profile index (KDPI) values were calculated as described for year 2017 (16). For the logistic regression models KDPI was categorized to quartiles, with the lowest quartile as the reference value. Variables were categorized due to the fact that the association with DGF was not linear throughout the distribution in the variables. In addition, donor age was modeled non-linearly as a continuous variable using fourth degree polynomial functions. When KDPI was included in the models, all the other donor factors used to calculate KDPI were left out of the model due to possible multi-collinearity (age, race, body mass index (BMI), history of hypertension, history of diabetes, and cause of death, DCD status). The interaction terms cold ischemia time * donor age, and cold ischemia * KDPI, were used to analyze whether the risk associated with cold ischemia differed according to age category or category of KDPI. In addition, the odds ratios associated with different cold ischemia time categories were analyzed separately in different age categories, and in different KDPI categories. As the use of machine perfusion has been associated with lower incidence of DGF and significant interaction was detected between donor age and the use of machine perfusion, analyses were performed also separately among kidneys transplanted after machine perfusion. UNOS and OPTN implemented a new kidney allocation system (KAS) in December 4th 2014, which may have potential impact on our findings. Therefore, sensitivity analyses were performed also separately in kidneys transplanted before or after the implementation of KAS.

Complete data were available for all other variables used for analysis, except for donor history of hypertension (missing from 587 patients), recipient diabetes history (missing from five), number of HLA mismatches (missing from 357), cold ischemia time (missing from 776), and cPRA (missing from 20 patients). Patients with missing data were left out of the respective analyses. The

calculations were performed with IBM SPSS statistical software (version 24.0, IBM Corporation, Somers, NY). Two-sided P-values <0.05 were considered statistically significant.

Results

A total of 90,717 recipients of deceased donor kidney transplantation were included in the analyses. The frequency of DGF was 29% in the whole cohort, 45% in kidneys from donors after circulatory death, and 25% in kidneys from donors after brain death (P<0.001). Patients with and without DGF are compared in table 1.

Association of donor age on the risk of DGF

Table 2 shows the results of the multivariable model analyzing the risk factors for DGF with regard to cold ischemia time and donor age. The final model was adjusted for recipient factors (age, race, gender, diabetes, last available cPRA, duration of pretransplant dialysis) and donor factors (cause of death, gender, race, BMI, creatinine, donation after circulatory death status, history of hypertension, and HLA mismatch). Detailed results of the multivariable model are shown in supplemental table 1 (Table S1). In the multivariable model, cold ischemia time (OR 1.02 per one hour increase, 95% CI 1.018-1.022) was an independent predictor of DGF. For the final model, cold ischemia time was categorized to 0-11hrs (reference group), 12-15 hours, 16-19 hours, 20-23 hours, and ≥24 hrs. To assess the statistical significance of the association of increased donor age on the risk of DGF, the oldest age group (donor age ≥65 years) was used as the reference group and the risk was analyzed with 5 years increments until the age categories 12-19, 5-11, and 0-4 years . Although clear association was seen between donor age and the risk of DGF, statistically significantly lower risk associated with younger donor age was not seen until with donor age <50 years, and the risk continued to be lower within each age category until donor age <12 years (table 2). The nonlinear association of donor age with the risk of DGF is graphically characterized in figure 1.

Association of machine perfusion

Machine perfusion is potentially a confounding factor when the association of donor age is analyzed, as the frequency of machine perfusion utilization increased with donor age and machine perfusion may be used more frequently in marginal donors with the highest risk of DGF. Among the whole study cohort, machine perfusion was employed in 33656 kidney transplantations (37%). The frequency was 26% in donors <20 years, 43% among donors between 45 and 64 years, and 49% among kidneys from donors ≥65 years of age. When the use of machine perfusion was included in the multivariable model, the use of machine perfusion was associated with a lower risk of DGF (OR 0.58, 95% CI 0.56-0.60, P<0.001). All other independent risk factors remained significant and the magnitude of effect remained within similar range. A statistically significant interaction was detected between donor age and the use of machine perfusion (P=0.001). Therefore, the association of donor age was analyzed separately among kidney transplants with or without machine perfusion in a similar multivariable model, shown in supplemental table 2. Among kidneys transplanted without machine perfusion, the association of donor age remained similar as in the whole cohort (table S2). Among kidneys transplanted with machine perfusion, statistically significantly lower risk of DGF was detected already in donors between the age 50-54 years, whereas no statistically significant difference in the risk of DGF was detected between kidneys from donors between 55 and 64 years compared to donors ≥65 years.

Association of cold ischemia on kidneys from older donors

The association of increased cold ischemia time with the risk of DGF was not higher in kidneys from older donors in any donor age category. No significant interaction was detected in the multivariable logistic regression between donor age and cold ischemia time (P=0.27). Frequencies of DGF in different donor age and cold ischemia categories are shown in table 3. Although both higher donor age and longer cold ischemia times were associated with higher risk of DGF, the risk

associated with longer cold ischemia times was not higher among the kidneys from older donors compared to younger donors. This was confirmed in a multivariable model (including the same variables as in table 2), where the odds ratios within the various cold ischemia categories remained virtually similar in all donor age categories, also in kidneys transplanted with or without machine perfusion (figure 2).

Association between KDPI and cold ischemia time with delayed graft function

When KDPIs were included in the logistic regression model (categorized to, 0-24% as the reference, compared to 25-49%, 50-74%, and 75% or more) to replace variables included in the KDPI, KDPI and cold ischemia time were both independently associated with higher risk of DGF (table 4A). Other risk factors for DGF (donor hypertension, donor high creatinine, donors after circulatory death, high cPRA, donor BMI, donor cause of death) remained significant (table S3). There was a statistically significant interaction between KDPI and cold ischemia time (P=0.008). The frequencies of DGF in different cold ischemia time and KDPI categories are shown in table 4B. Although the frequency of DGF was higher with both KDPI and with increasing cold ischemia times, no clinically relevant increase in the association between cold ischemia time and DGF risk could be observed among the kidneys from high KDPI donors. This was confirmed in a multivariable model (including the same variables as in table 4A), where the odds ratios of the various cold ischemia categories remained in the same range in all KDPI categories (figure 3).

Sensitivity analyses

To investigate the most important findings of this study in more detail, the same analyses were repeated in different subgroups as sensitivity analyses. As the effect of donor age may be different among donors after circulatory death, we studied the association of donor age with DGF separately among donation after circulatory death and donation after brain death donor kidneys. Among kidneys from donors after brain death, the results of the multivariable logistic regression model

(including the same variables as in table 2) were similar enough to draw the same conclusions as from the whole cohort (table S4). Among the 16213 kidneys from donors after circulatory death, the association of increased donor age was comparable to the whole cohort, as the risk of DGF was not statistically significantly lower until donors younger than 35 years compared to donors ≥65 years (OR 0.54, 95% CI 0.30-0.96, P=0.04 for donors aged 30-34 years, table S4). When kidneys transplanted before or after the Kidney Allocation System were analyzed separately, the association of donor age with the risk of DGF supported our findings from the whole cohort. Among kidneys transplanted before KAS, lower risk of DGF associated with younger donor age reached statistical significance only among donors <45 years of age (OR 0.82, 95% CI 0.72-0.94, P=0.005 for donors aged 40-44 years) compared to donors ≥65 years, whereas among kidney transplanted after KAS, statistically significantly lower risk of DGF associated with donor age was seen among kidneys transplanted from donors <50 years of age (OR 0.80, 95% CI 0.69-0.93, P=0.005). The other risk factors associated with the risk of DGF remained significant in the models, and the association between cold ischemia time and DGF remained similar in all age and KDPI categories (table S5).

During the study period, altogether 12383 patients received a deceased donor kidney transplantation preemptively without preceding dialysis treatment. As the definition of DGF in this study was the need for dialysis during the first posttransplant week, patients with preemptive transplantation were excluded from the primary analyses. Among the 12383 patients with preemptive transplantation, the frequency of DGF with the current definition was 7% (1027 patients). When these patients with preemptive transplantation were included in the cohort, the results of the multivariable model remained unchanged with regard to the association of donor age and cold ischemia time with the risk of DGF (table S6).

DISCUSSION

In this study analyzing a large number of kidney transplants from the current era in the US, our main finding was that although higher donor age is independently associated with higher risk of DGF, the effect of age becomes less pronounced when donor age exceeds 50 years. In fact, the risk of DGF for donor age groups between 50 and 64 years were not statistically different compared to the reference group of donor age of more than 65 years. In addition, no increased susceptibility of older kidneys to harmful effect of cold storage was found in terms of DGF risk. Similarly, when low organ quality was assessed by means of KDPI value instead of donor age, although a statistically significant interaction with cold ischemia time was found, we did not observe a practically meaningful increase in the susceptibility of lower quality kidneys to cold ischemia.

In all studies addressing the risk of DGF after deceased donor kidney transplantation, increased cold ischemia time and high donor age have been major risk factors (7), and prolonged cold storage has been considered especially harmful to kidneys from older donors (18-20). Within transplant organizations, such as Eurotransplant Senior Program, organ allocation policies have been designed to minimize cold ischemia time in older donors based on this assumption (21). The aim of our current study was to examine the association of cold ischemia and DGF in detail, and in contrast to previous literature, our findings do not support higher risk of DGF for older donor or marginal kidneys with prolonged cold ischemia time. Although donor age is an important risk factor for DGF, the differences were not statistically significant beyond donor age of 50 years, compared to the oldest age group. The reasons for the difference in the association of donor age with the risk of DGF in our current study and previous literature can only be speculated. Average life expectancy increases in all developed countries, also allowing individuals to live healthier for longer than previously. Therefore, other factors than biological age, most importantly comorbidities, may play a more important role also in the risk of DGF. Indeed, donor history of hypertension, donor kidney function, and donor BMI were all associated with increased risk of DGF in our study, possibly diluting the individual effect of donor age. However, although the association was not amplified in old or marginal donors, longer cold ischemia time was still associated with higher risk

of DGF, and this may have potential impact on long-term survival of the grafts or graft function. Therefore, organ allocation policies may still need to be directed to prevent this cumulative damage to more compromised kidneys from older or marginal donors.

Average donor age has not increased in the US in the recent years, and less than 25% of the deceased donors have been >50 years of age (22). This is in sharp contrast with many European countries, where e.g. within the Eurotransplant in 2017, 47% of deceased kidney donors were older than 55 years and 23% of donors were 65 years or older (23). Only 7% of the deceased donors in our current study were 65 years or older, and the lower relative utilization of older donors in the US possibly leads to selection of healthier old donors with less comorbidities. Difference in age distribution between various kidney transplant cohorts may be one factor explaining the varying impact of donor age on the risk of DGF in earlier studies. Therefore, the results may not be directly applicable to other transplant cohorts.

Although delayed graft function commonly complicates deceased donor kidney transplantation, relatively little research focus has been directed to risk factors of DGF in the recent years, not to mention the optimal treatment strategies after occurrence of DGF. Although the impact of DGF on long-term graft prognosis has been questioned (8,9), DGF is associated with higher risk of acute rejection, morbidity, length of hospital stay, and higher costs after transplantation (4-6). The frequency or duration of DGF can be addressed from several directions, including optimal treatment of the deceased donor (24,25), strategies to minimize cold ischemia times (26), the optimal utilization of machine perfusion (27), or optimal dialysis strategy after occurrence of DGF (28).

The use of induction therapy, especially lymphocyte-depleting induction, has been associated with lower incidence of delayed graft function in several studies (29-31), although a recent Cochrane systematic review failed to show any benefit of induction therapy in terms of DGF risk (32). Our analyses were not adjusted for data regarding induction therapy, which may limit our conclusions. On the other hand, according to OPTN/SRTR Annual Data Report 2016, induction therapy was used on approximately 90% of kidney transplantations in the US, and T-cell depleting agents in

>70% of the patients (22). Similarly, some studies have failed to show any difference in the risk of DGF between IL-2R- antagonists and lymphocyte depleting agents (33). Therefore, the possible confounding effect of induction therapy in our current analyses is likely small. However, the increasing use of induction therapy compared to earlier studies may be one factor contributing to the lower importance of donor age on the risk of DGF.

This study has some limitations of note. Several studies have shown that longer cold ischemia time is associated with higher risk of graft failure (34, 35), independent of the occurrence of DGF. We did not, however, analyze the impact of donor age on graft survival, as our aim was to analyze risk factors associated only with DGF, not long-term prognosis, and to focus specifically on the association of donor age and cold ischemia time. KDPI was used to characterize the marginality of donors in this study, although KDPI and KAS were introduced only in 2014. For a significant proportion of patients in this study KDPI is calculated only retrospectively, and was not used in organ allocation at the time of transplantation, which may limit the generalizability of the results. Lastly, causality between explanatory variables and DGF cannot be concluded from this observational registry analysis, as there may be known or unknown confounding factors that were not adjusted for.

Conclusions

The association of old donor age on the risk of DGF was less prominent than previously reported, and the relative increase in the risk of DGF associated with longer cold ischemia time was not higher among kidneys from older or higher KDPI donors. Our data suggest that other factors than only old donor age play a role in the development of delayed graft function after kidney transplantation in the current era.

Disclosures

The authors declare no conflicts of interest. The data reported here have been supplied by the Minneapolis Medical Research Foundation (MMRF) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government. The data that support the findings of this study are available from SRTR. Restrictions apply to the availability of these data, which were used under license for this study.

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Supplemental material table of contents:

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Table 1. Characterization of patients included in the study, transplanted between 2010 and September 2018 in the US. (DGF = Delayed graft function; BMI=Body mass index). Mean ± 1 SD, unless otherwise indicated.

	Patients with DGF (N=26066)	**Patients without DGF (N=64651)**
Recipient age (yrs)	54 ± 13	50 ± 16
Recipient male	17545 (67%)	37743 (58%)
Recipient diabetes	11019 (42%)	21072 (33%)
Black recipients	10122 (39%)	21037 (33%)
cPRA 0-79	21928 (84%)	53358 (83%)
80-94	1791 (7%)	5384 (8%)
95-98	924 (4%)	2607 (4%)
≥99 %	1416 (5%)	3288 (5%)
Donor age categories		
0-29	6531 (25%)	24067 (37%)
30-44	7366 (28%)	17546 (27%)
45-64	9971 (38%)	18574 (28%)
≥65	2198 (8%)	4464 (7%)
Donor male	16362 (63%)	38849 (60%)
Donor BMI	29 ± 7	27 ± 7
Donation after circulatory death donors	7216 (28%)	8980 (14%)
Machine perfusion	9584 (37%)	24034 (37%)
Black donors	3728 (15%)	9734 (15%)
Expanded criteria donor	4496 (17%)	8335 (13%)
Donor serum creatinine >1.5mg/dL	7037 (27%)	9328 (14%)
Donor history of hypertension	8894 (34%)	15822 (25%)
KDPI >80%	4738 (18%)	8179 (13%)
Cold ischemia time		
<12 hrs	5748 (22%)	20934 (33%)
12-15 hrs	4726 (18%)	12642 (20%)
16-19 hrs	4882 (19%)	11334 (18%)
20-23 hrs	4087 (16%)	8084 (13%)
≥ 24 hrs	6444 (25%)	11089 (18%)
Number of HLA mismatches	4 ± 2	4 ± 2

Table 2. The risk of delayed graft function associated with donor age and cold ischemia time, among the 90717 patients transplanted between 2010 and September 2018. Model adjusted for DCD status, recipient age and gender, recipient diabetes, recipient race, calculated panel-reactive antibodies (cPRA), pretransplant dialysis duration, donor cause of death, donor race, donor history of hypertension, donor creatinine, donor BMI, and number of HLA mismatches.

	OR	**95% CI**
Donor age (reference ≥ 65 years)		
60-64	0.97	0.87-1.09
55-59	0.93	0.84-1.03
50-54	0.90	0.82-1.00
45-49	0.89	0.81-0.99
40-44	0.80	0.72-0.88
35-39	0.74	0.66-0.82
30-34	0.66	0.59-0.73
25-29	0.63	0.56-0.69
20-24	0.57	0.51-0.64
12-19	0.54	0.48-0.60
5-11	0.67	0.58-0.78
0-4	0.76	0.65-0.87
Cold ischemia time (reference <12 hrs)		
12-15 hrs	1.20	1.15-1.26
16-19 hrs	1.27	1.21-1.33
20-23 hrs	1.47	1.40-1.55
24 hrs +	1.70	1.63-1.78

Table 3. The frequency of delayed graft function in categories of cold ischemia time and donor age.

Cold ischemia time	Donor age 0-29	Donor age 30-44	Donor age 45-64	Donor age 65-
<12 hrs	15%	23%	27%	27%
12-15 hrs	20%	28%	33%	33%
16-19 hrs	23%	32%	36%	32%
20-23 hrs	26%	35%	39%	37%
24+ hrs	30%	37%	43%	38%

Table 4.

A) The association of kidney donor profile index (KDPI) and cold ischemia time with the risk of delayed graft function (model adjusted for cPRA, cold ischemia time, recipient age and gender, recipient diabetes, recipient race, pretransplant dialysis duration, donor gender, number of HLA mismatches, and KDPI categories.)

B) The frequency of delayed graft function in categories of cold ischemia time and kidney donor profile index (KDPI).

A)	**OR**	**95% CI**
KDPI (reference <25 %)		
25-49 %	1.58	1.51-1.65
50-74	2.03	1.94-2.12
≥ 75 %	2.15	2.05-2.26
Cold ischemia time (reference <12 hrs)		
12-15 hrs	1.29	1.24-1.36
16-19 hrs	1.45	1.38-1.52
20-23 hrs	1.71	1.62-1.79
24+ hrs	1.95	1.87-2.04

B)

Cold Ischemia time	KDPI 0-24%	KDPI 25-49%	KDPI 50-74%	KDPI 75-100%
<12 hrs	14%	22%	27%	29%
12-15 hrs	18%	28%	31%	35%
16-19 hrs	20%	31%	34%	36%
20-23 hrs	22%	33%	39%	40%
24+ hrs	25%	35%	43%	42%

Figure Legends

Figure 1. Graphical representation of the association between donor age and the risk of delayed graft function. Risk of delayed graft function associated with donor age is expressed as odds ratios for categories of donor age (black line, 95% confidence intervals expressed as dashed lines; reference group >65 years).In addition, odds ratios for donor age as a continuous variable using fourth degree polynomial logistic regression equations were used to describe the nonlinear association between donor age and the risk of delayed graft function (red line; reference age > 65 years). Associations were analyzed in a multivariable logistic regression model adjusted for cPRA, donor after circulatory death status, recipient age and gender, recipient diabetes, recipient race, pretransplant dialysis duration, donor race, donor history of hypertension, donor creatinine, donor BMI, donor cause of death, and number of HLA mismatches

Figure 2. Graphical representation of the association between cold ischemia time and the risk of delayed graft function in various donor age categories. The risk of delayed graft function in categories of donor age and cold ischemia time is expressed as odds ratios (colored lines for different donor age catecories; odds ratios and 95% confidence intervals in the table), analyzed in a multivariable logistic regression model adjusted for cPRA, donor after circulatory death status, recipient age and gender, recipient diabetes, recipient race, pretransplant dialysis duration, donor race, donor history of hypertension, donor creatinine, donor BMI, donor cause of death, and number of HLA mismatches. **A)** All patients; **B)** Kidneys transplanted without machine perfusion; **C)** Kidneys transplanted with machine perfusion.

Figure 3. Graphical representation of the association between cold ischemia time and the risk of delayed graft function in various kidney donor profile index (KDPI) categories. The risk of delayed graft function in categories of kidney donor profile index (KDPI) and cold ischemia time is expressed as odds ratios (colored lines for different KDPI catecories; odds ratios and 95%

confidence intervals in the table), analyzed in a multivariable logistic regression model adjusted for cPRA, cold ischemia time, recipient age and gender, recipient diabetes, recipient race, pretransplant dialysis duration, donor gender, and number of HLA mismatches.

Supplemental material table of contents:

Table S1. Results of the multivariable model of risk factors associated with delayed graft function after deceased donor kidney transplantation. Donor age categories and cold ischemia time categories are included in the model, but presented in table 2.

	OR	95% CI
last cPRA (reference <80%)		
80-94%	1.04	0.98-1.10
95-98%	1.14	1.05-1.24
99-100%	1.33	1.24-1.43
DCD	2.66	2.56-2.77
Recipient age (years)	1.002	1.001-1.003
Recipient diabetes	1.35	1.31-1.40
Recipient female gender	0.68	0.66-0.71
Recipient black race	1.26	1.22-1.30
Donor female gender	0.90	0.87-0.93
Donor black race	0.88	0.84-0.92
Donor history of hypertension	1.17	1.13-1.22
Donor BMI (kg/m^2)	1.02	1.01-1.02
Donor creatinine >1.5 mg/dL	2.36	2.27-2.46
Number of HLA mismatches	1.03	1.02-1.04
Donor cerebrovascular cause of death	1.13	1.09-1.17
Duration of pretransplant dialysis (years)	1.07	1.06-1.08

Table S2. The risk of delayed graft function associated with donor age in kidneys transplanted with or without machine perfusion. Model adjusted for cPRA, cold ischemia time, DCD status, recipient age and gender, recipient diabetes, recipient race, pretransplant dialysis duration, donor race, donor history of hypertension, donor creatinine, donor BMI, donor cause of death, and number of HLA mismatches.

	OR	95% CI
Kidneys transplanted without machine perfusion		
Donor age (reference ≥ 65 years)		
60-64	0.99	0.85-1.15
55-59	0.92	0.80-1.06
50-54	0.89	0.77-1.02
45-49	0.89	0.79-1.03
40-44	0.81	0.70-0.93
35-39	0.70	0.61-0.80
30-34	0.62	0.53-0.71
25-29	0.61	0.53-0.70
20-24	0.54	0.47-0.62
12-19	0.49	0.42-0.57
5-11	0.59	0.50-0.71
0-4	0.65	0.54-0.77
Kidneys transplanted with machine perfusion		
Donor age (reference ≥ 65 years)		
60-64	0.93	0.79-1.10
55-59	0.87	0.75-1.01
50-54	0.84	0.73-0.98
45-49	0.76	0.65-0.89
40-44	0.65	0.56-0.76
35-39	0.68	0.58-0.79
30-34	0.61	0.52-0.72
25-29	0.52	0.44-0.61
20-24	0.50	0.43-0.60
12-19	0.52	0.44-0.62
5-11	0.58	0.43-0.79
0-4	0.67	0.50-0.91

cPRA, calculated panel-reactive antibodies; DCD, donation after circulatory death.

Table S3. Results of the multivariable model of risk factors associated with delayed graft function after deceased donor kidney transplantation, including Kidney Donor Profile Index in the model. In addition to KDPI, model is adjusted for cPRA, cold ischemia time, recipient age and gender, recipient diabetes, recipient race, pretransplant dialysis duration, donor gender, number of HLA mismatches. Cold ischemia time and KDPI categories data are presented in table 4.

	OR	95% CI
last cPRA (reference <80%)		
80-94%	1.02	0.96-1.08
95-98%	1.08	1.00-1.18
99-100%	1.17	1.09-1.25
Recipient age (years)	1.004	1.002-1.005
Recipient diabetes	1.34	1.30-1.39
Recipient female gender	0.69	0.67-0.71
Recipient black race	1.20	1.16-1.24
Donor female gender	0.79	0.77-0.82
Number of HLA mismatches	1.03	1.01-1.04
Duration of pretransplant dialysis (years)	1.07	1.06-1.08

Table S4. The risk of delayed graft function associated with donor age in kidneys transplanted from donors after brain death (A), or donors after circulatory death (B). Model is adjusted for cPRA, cold ischemia time, recipient age and gender, recipient diabetes, recipient race, pretransplant dialysis duration, donor race, donor history of hypertension, donor creatinine, donor BMI, donor cause of death, and number of HLA mismatches.

	OR	95% CI
A) Kidneys transplanted from donors after brain death		
Donor age (reference ≥ 65 years)		
60-64	0.97	0.87-1.09
55-59	0.91	0.82-1.01
50-54	0.91	0.82-1.01
45-49	0.90	0.81-1.01
40-44	0.82	0.74-0.92
35-39	0.73	0.65-0.81
30-34	0.68	0.61-0.77
25-29	0.62	0.56-0.70
20-24	0.58	0.52-0.66
12-19	0.57	0.51-0.64
5-11	0.74	0.63-0.86
0-4	0.81	0.70-0.95
B) Kidneys transplanted from donors after circulatory death		
Donor age (reference ≥ 65 years)		
60-64	0.83	0.46-1.53
55-59	0.85	0.45-1.51
50-54	0.75	0.42-1.33
45-49	0.73	0.41-1.30
40-44	0.61	0.34-1.09
35-39	0.64	0.36-1.14
30-34	0.54	0.30-0.96
25-29	0.52	0.29-0.94
20-24	0.46	0.26-0.82
12-19	0.40	0.22-0.72
5-11	0.41	0.22-0.77
0-4	0.49	0.26-0.91

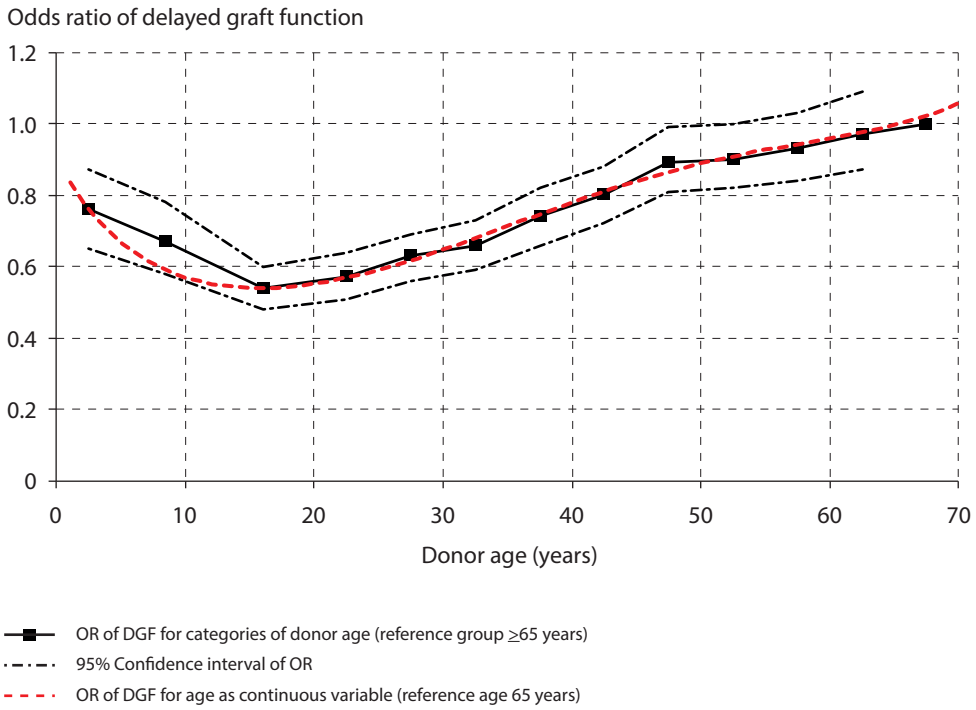
Table S5. The risk of delayed graft function in categories of cold ischemia time and donor age, or categories of cold ischemia time and kidney donor profile index (KDPI), analyzed in a multivariable model, expressed as odds ratios and 95% confidence intervals (adjusted for cPRA, DCD status, recipient age and gender, recipient diabetes, recipient race, donor race, donor history of hypertension, donor creatinine, donor BMI, donor cause of death, and number of HLA mismatches). **A)** In kidneys transplanted before (N=47726) or **B)** after the implementation of Kidney Allocation System (KAS) in December 2014 (N=42991).

A) Kidneys transplanted before implementation of kidney allocation system (KAS)				
Cold Ischemia time (reference 0-11 hrs)	Donor age 0-29	Donor age 30-44	Donor age 45-64	Donor age 65+
12-15 hrs	1.30 (1.15-1.47)	1.27 (1.12-1.44)	1.26 (1.13-1.40)	1.23 (0.99-1.53)
16-19 hrs	1.40 (1.23-1.58)	1.40 (1.24-1.59)	1.27 (1.14-1.42)	1.15 (0.92-1.44)
20-23 hrs	1.60 (1.40-1.83)	1.47 (1.28-1.70)	1.58 (1.40-1.78)	1.51 (1.19-1.93)
24- hrs	1.92 (1.71-2.17)	1.59 (1.41-1.81)	1.76 (1.58-1.95)	1.59 (1.28-1.97)
Cold ischemia time (reference 0-11 hrs)	KDPI 0-24	KDPI 25-49	KDPI 50-74	KDPI ≥75
12-15 hrs	1.25 (1.09-1.43)	1.42 (1.25-1.60)	1.15 (1.02-1.30)	1.28 (1.11-1.47)
16-19 hrs	1.38 (1.19-1.59)	1.49 (1.31-1.69)	1.27 (1.12-1.43)	1.16 (1.01-1.33)
20-23 hrs	1.58 (1.35-1.86)	1.62 (1.41-1.86)	1.46 (1.28-1.66)	1.49 (1.29-1.74)
24- hrs	1.68 (1.45-1.94)	1.83 (1.62-2.07)	1.67 (1.49-1.88)	1.68 (1.48-1.91)
B) Kidneys transplanted after implementation of kidney allocation system (KAS)				
Cold Ischemia time (reference 0-11 hrs)	Donor age 0-29	Donor age 30-44	Donor age 45-64	Donor age 65+
12-15 hrs	1.12 (0.98-1.27)	1.11 (0.90-1.24)	1.12 (0.99-1.27)	1.17 (0.89-1.52)
16-19 hrs	1.19 (1.04-1.35)	1.28 (1.15-1.45)	1.19 (1.06-1.34)	1.05 (0.81-1.36)
20-23 hrs	1.41 (1.23-1.63)	1.50 (1.32-1.71)	1.28 (1.13-1.45)	1.36 (1.03-1.79)
24- hrs	1.73 (1.53-1.96)	1.71 (1.52-1.93)	1.62 (1.45-1.81)	1.45 (1.13-1.86)
Cold ischemia time (reference 0-11 hrs)	KDPI 0-24	KDPI 25-49	KDPI 50-74	KDPI ≥75
12-15 hrs	1.17 (1.01-1.35)	1.10 (0.97-1.25)	1.01 (0.89-1.14)	1.21 (1.03-1.42)
16-19 hrs	1.09 (0.94-1.27)	1.31 (1.16-1.49)	1.11 (0.98-1.26)	1.21 (1.03-1.42)
20-23 hrs	1.30 (1.09-1.54)	1.36 (1.19-1.56)	1.38 (1.21-1.57)	1.39 (1.18-1.64)
24- hrs	1.68 (1.45-1.96)	1.57 (1.39-1.77)	1.72 (1.53-1.94)	1.55 (1.34-1.80)

Table S6. The risk of delayed graft function associated with donor age and cold ischemia time, among the 103100 patients transplanted between 2010 and September 2018, including also 12383 patients transplanted preemptively without preceding dialysis treatment. Model adjusted for DCD status, recipient age and gender, recipient diabetes, recipient race, calculated panel-reactive antibodies (cPRA), pretransplant dialysis duration, donor cause of death, donor race, donor history of hypertension, donor creatinine, donor BMI, and number of HLA mismatches.

	OR	**95% CI**
Donor age (reference ≥ 65 years)		
60-64	1.01	0.91-1.12
55-59	0.99	0.90-1.10
50-54	0.97	0.88-1.06
45-49	0.97	0.88-1.06
40-44	0.87	0.79-0.96
35-39	0.80	0.73-0.89
30-34	0.69	0.62-0.76
25-29	0.63	0.57-0.69
20-24	0.56	0.51-0.62
12-19	0.51	0.45-0.56
5-11	0.57	0.50-0.66
0-4	0.70	0.61-0.81
Cold ischemia time (reference <12 hrs)		
12-15 hrs	1.22	1.16-1.27
16-19 hrs	1.29	1.24-1.36
20-23 hrs	1.48	1.40-1.55
24 hrs +	1.67	1.60-1.74

Figure 1


Odds ratio of delayed graft function
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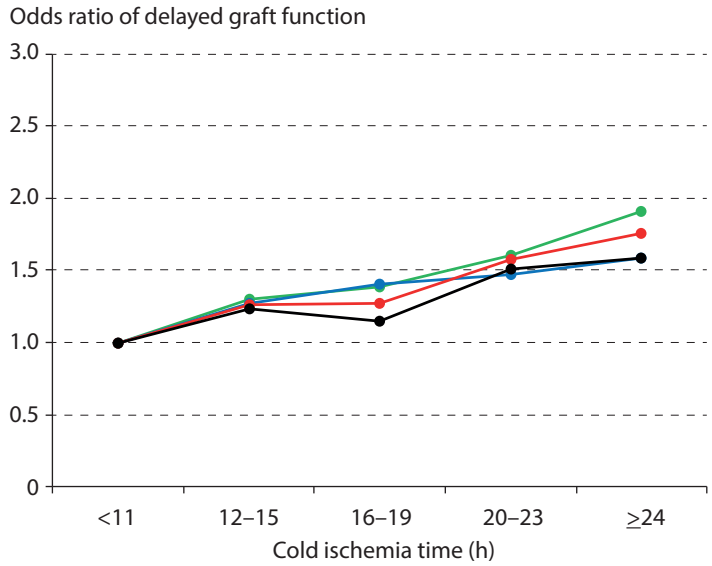
1.0
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
Donor age (years)
OR of DGF for categories of donor age (reference group ≥65 years)
95% Confidence interval of OR
OR of DGF for age as continuous variable (reference age 65 years)

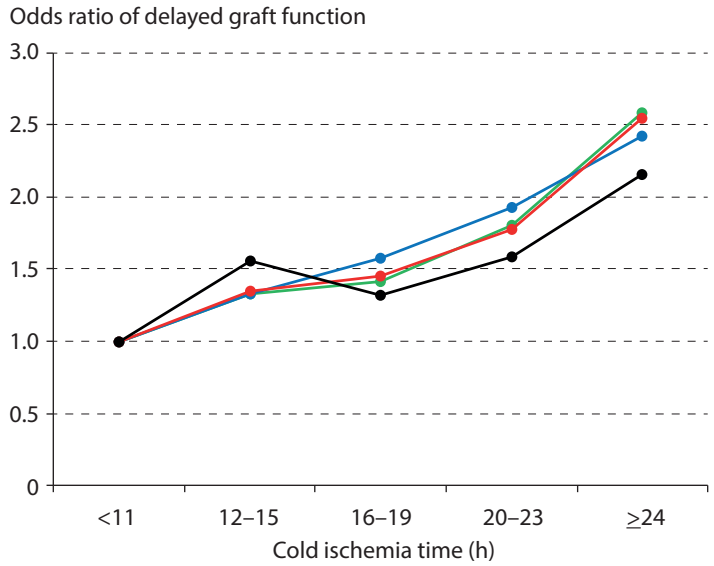
Figure 2A



OR of DGF (95% confidence interval)					
Donor age <30 y	1	1.30 (1.15–1.46)	1.39 (1.22–1.57)	1.60 (1.39–1.82)	1.91 (1.70–2.15)
Donor age 30–44 y	1	1.27 (1.12–1.44)	1.40 (1.24–1.59)	1.47 (1.28–1.70)	1.59 (1.41–1.81)
Donor age 45–64 y	1	1.26 (1.13–1.40)	1.27 (1.14–1.42)	1.58 (1.40–1.78)	1.76 (1.58–1.95)
Donor age ≥65 y	1	1.23 (0.99–1.53)	1.15 (0.92–1.44)	1.51 (1.19–1.97)	1.59 (1.28–1.97)

Figure 2B

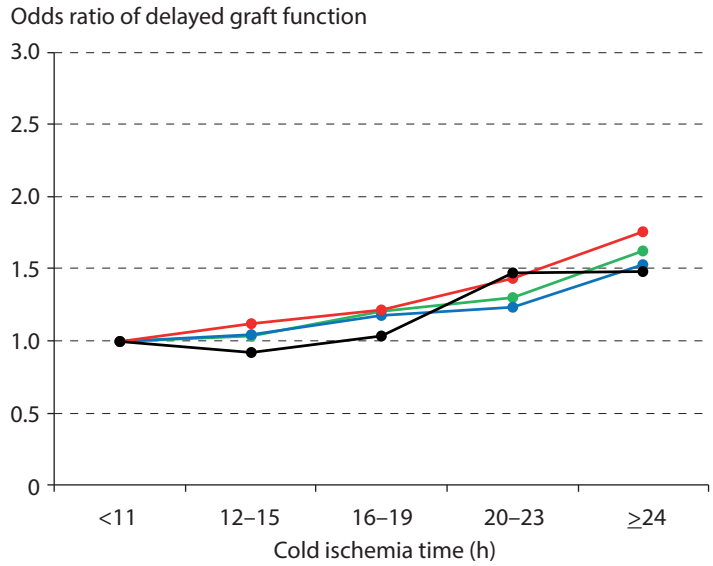
Without machine perfusion



OR of DGF (95% confidence interval)					
Donor age <30 y	1	1.33 (1.21–1.47)	1.41 (1.27–1.57)	1.80 (1.61–2.03)	2.58 (2.31–2.88)
Donor age 30–44 y	1	1.33 (1.20–1.47)	1.58 (1.42–1.76)	1.93 (1.71–2.17)	2.42 (2.13–2.71)
Donor age 45–64 y	1	1.35 (1.23–1.48)	1.45 (1.31–1.60)	1.78 (1.59–1.99)	2.55 (2.23–2.85)
Donor age ≥65 y	1	1.56 (1.27–1.93)	1.32 (1.06–1.64)	1.59 (1.25–2.02)	2.16 (1.71–2.73)

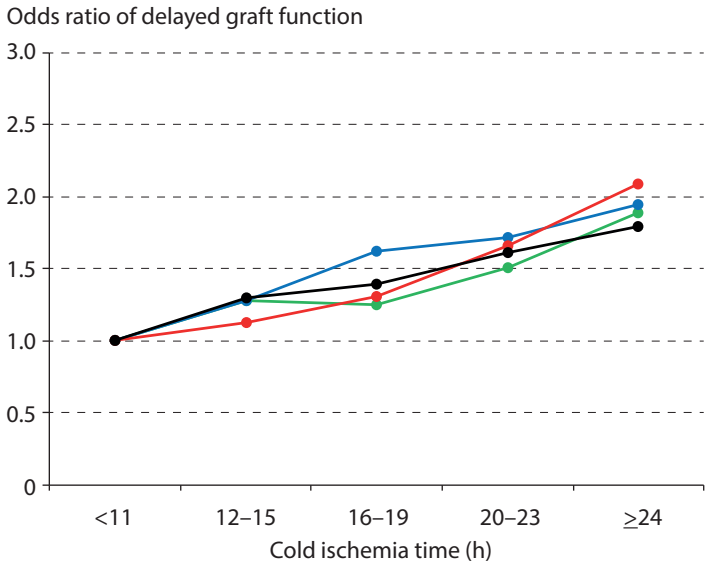
Figure 2C

With machine perfusion



OR of DGF (95% confidence interval)					
Donor age <30 y	1	1.03 (0.84–1.26)	1.20 (0.99–1.46)	1.30 (1.06–1.58)	1.62 (1.35–1.93)
Donor age 30–44 y	1	1.04 (0.87–1.24)	1.18 (1.00–1.41)	1.23 (1.03–1.47)	1.53 (1.31–1.80)
Donor age 45–64 y	1	1.12 (0.96–1.30)	1.21 (1.04–1.40)	1.43 (1.23–1.66)	1.76 (1.54–2.01)
Donor age ≥65 y	1	0.92 (0.68–1.24)	1.03 (0.77–1.37)	1.47 (1.09–1.99)	1.48 (1.13–1.94)

Figure 3



OR of DGF (95% confidence interval)					
KDPI 0–24	1	1.28 (1.11–1.48)	1.25 (1.08–1.45)	1.51 (1.28–1.78)	1.89 (1.64–2.19)
KDPI 25–49	1	1.28 (1.13–1.45)	1.62 (1.43–1.82)	1.72 (1.51–1.96)	1.95 (1.73–2.20)
KDPI 50–74	1	1.13 (1.00–1.27)	1.31 (1.16–1.48)	1.66 (1.47–1.89)	2.09 (1.86–2.34)
KDPI ≥75	1	1.30 (1.11–1.53)	1.39 (1.19–1.63)	1.61 (1.37–1.89)	1.79 (1.55–2.07)